EXHIBIT 82

Trends in Mesothelioma Incidence in the United States and the Forecast Epidemic Due to Asbestos Exposure During World War II

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The incidence of mesothelioma in those not exposed to asbestos is of the order of one per million per annum; however, among men heavily exposed to asbestos, the risk may be increased by a factor of 1000 or more. About 1000 cases are now diagnosed each year in the United States, and it has been suggested that increasing asbestos exposure, particularly in shipyards and other industries that flourished during World War II, may result in very much higher rates in the near future. We have tried to produce more formal estimates of the pattern of past exposure and the likely evolution of future incidence by combining incidence patterns observed in industrial cohorts with the results of a survey of cases diagnosed in Los Angeles County in which age and year of first exposure to asbestos were ascertained. Our results suggest that the extent of shipyard and other wartime exposure has been grossly exaggerated, although the effects of more recent exposure may be greater than is generally appreciated. In particular, it seems that the total number of mesotheliomas caused by shipyard exposure during World War II is likely to be about 5000, almost half of which have already occurred.

Projections of future numbers are based on classification of the population into cohorts first exposed to asbestos at different ages in each period. These subgroups are not observed directly, however, and our results do not provide estimates of risk that can be applied usefully to identifiable individuals. A formal account of this unusual method of analysis is given in the Appendix of this paper but the results are presented in a less formal but hopefully more comprehensible form within the text.

THE AGE AND TIME DEPENDENCE OF MESOTHELIOMA CAUSED BY ASBESTOS EXPOSURE

The proportion of mesotheliomas in asbestos workers that are peritoneal in origin varies widely under different conditions. Among North American

insulation workers who have been exposed to amosite, a high proportion are peritoneal, but the majority of mesotheliomas are pleural among miners and factory workers exposed only to chrysotile or crocidolite. For both practical and theoretical purposes, however, the two sites can be amalgamated. Both diseases are quickly fatal, and the incidence of cases caused by asbestos exposure for both appears to be approximately proportional to the 3.5th power of time since first exposure, irrespective of age at first exposure, duration of exposure, or fiber type (Peto et al. 1981). North American insulation workers provide the only substantial data on incidence beyond 40 years after first exposure, but other cohorts followed up for shorter periods conform to the same incidence pattern (Peto et al. 1981). Therefore, we have assumed that incidence will continue to increase as (time since first exposure)$^{3.5}$ indefinitely in the following analyses, but deaths occurring after age 80 are ignored in the resulting predictions of future mesothelioma incidence. Projection beyond this age would entail extrapolation beyond the range of observation in any existing cohort and probably could not be tested, as misdiagnosis is common in extreme old age.

THE RELATIONSHIP BETWEEN CURRENT AND FUTURE MESOTHELIOMA INCIDENCE

Table 1 shows the numbers of cases that would be expected to occur in successive quinquennia up to age 80 among equal cohorts of men first exposed at various ages. The median ages at first exposure (18½, 23½, 28½, etc.) have been chosen so that each entry in Table 1 corresponds to a conventional age group and period of first exposure in our survey (see Table 2 below). Thus, for example, men first exposed at age 23½ in mid-1942 (the middle of the 1940-1944 period) would have been aged 55-59 in 1974-1978. Apart from an arbitrary multiplying factor, the figures in Table 1 are the product of (time since first exposure)$^{3.5}$ and the appropriate life-table for men in the United States. They are based on two assumptions: (1) that mesothelioma incidence continues to rise as (time since first exposure)$^{3.5}$ up to age 80, and (2) that overall age-specific mortality in exposed workers is similar to that of other men of the same age in the United States. Therefore, predictions of the future rate of increase based on these figures might be somewhat exaggerated, as mortality in heavily exposed asbestos workers is higher than in the general population. The proportion surviving may fall progressively below the survival curve based on national mortality figures, and there would then be proportionately fewer mesotheliomas in the future.

The last row in Table 1, giving the cumulative risk of developing mesothelioma by age 80, illustrates the enormous effect of age at first exposure. A man first exposed below age 20 suffers more than 10 times the risk of a man aged over 40, for example, and the assumed distribution of age at first exposure may substantially affect predictions of future risk.

Table 1
Predicted Numbers of Mesotheliomas That Would Occur among a Given Number of Men in Each Quinquennium Following First Exposre to Asbestos at a Fixed Level, by Age at First Exposure

	Age first exposed							
	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55
	Median age first exposed							
	18½	23½	28½	33½	38½	43½	48½	53½
Age at diagnosis	Predicted numbers of mesotheliomas							
25-29	.04							
30-34	.17	.04						
35-39	.48	.17	.04					
40-44	1.07	.47	.16	.04				
45-49	2.02	1.05	.47	.16	.03			
50-54	*3.40*	1.97	1.02	.46	.16	.03		
55-59	5.19	*3.24*	1.87	.97	.43	.15	.03	
60-64	7.22	4.77	*2.98*	1.72	.90	.40	.14	.03
65-69	9.12	6.31	4.17	*2.60*	1.51	.79	.36	.13
70-74	10.32	7.40	5.12	3.39	*2.12*	1.23	.65	.30
75-79	10.15	7.50	5.39	3.73	2.47	*1.55*	.91	.49
Total below age 80	49.18	32.92	21.22	13.07	7.62	4.15	2.09	0.95

Figures corresponding to cases occurring in 1974-1978 in men first exposed in 1942 are italicized.

MESOTHELIOMA INCIDENCE IN LOS ANGELES COUNTY AND IN THE UNITED STATES

The case or a close relative was interviewed in 87% (101/116) of male and 81% (25/31) of female pleural or peritoneal mesotheliomas diagnosed in Los Angeles County in 1974-1978, a period in which ascertainment probably was very close to complete. Exposure to asbestos was reported for 69 of the men for whom an interview was obtained; 22 reported no exposure, and in the remaining 10 it could not be determined if exposure had occurred. The 69 men with recorded asbestos exposure are tabulated according to age at first exposure and year of first exposure in Table 2. The 18 men first exposed in shipyards during World War II (1939-1945) are shown separately, both because the effects of such exposure are of particular interest and because they appear to have been rather older at first exposure than other men. The remaining 51 exposed men include only four shipyard workers.

Table 2
69 Male Mesotheliomas with Dated Asbestos Exposure Diagnosed in Los Angeles County in 1974-1978

Year first exposed	Age at first exposure to asbestos							
	16-20	21-25	26-30	31-35	36-40	41-45	over 45	Total
1915-1919	1	0						1
1920-1924	3	0	1					4
1925-1929	2	1	2	0				5
1930-1934	0	0	1	1	0			2
1935-1939	3	1	4	1	0	0		9
1940-1944	1	3	1	1	2	0	0	8
1945-1949	1	4	0	2	2	3	1	13
1950-1954	1	0	1	2	0	0	0	4
1955-1959	0	1	1	0	1	0	0	3
1960-1964	0	0	0	0	0	1	0	1
1965-1969	0	0	0	0	0	0	1	1
Total except WW II shipyard	12	10	11	7	5	4	2	51
1939-1945 (WW II shipyard)	1	2	2	4	3	4	2	18

Cases originating in World War II shipyard exposure are not included in the upper part of the table.

The incidence of mesothelioma in Los Angeles County in 1974-1978 was similar in both sexes to that observed in eight Surveillance, Epidemiology, and End Results Program (SEER) cancer registries between 1970 and 1976, except perhaps in the older age groups, where rates were rather higher among men and lower among women (Table 3). Based on these average rates, Hinds (1978) has estimated that approximately 900 cases were occurring each year in the United States between 1970 and 1976, of which almost 700 were in men. It appears that incidence was still rising during this period, however, and we shall assume that a total of 4000 male cases (800 per annum) were diagnosed in the United States between 1974 and 1978 as a basis for projections of national incidence.

Among the 91 men in our survey for whom adequate histories were obtained, 20% (18/91) were World War II shipyard workers, 56% (51/91) were first exposed to asbestos in other environments, and 24% (22/91) had never been exposed to asbestos. If this pattern is typical of the whole United States, approximately 800 World War II shipyard workers (20% of 4000), 2240 men with other asbestos exposure (56% of 4000), and 960 unexposed men (24% of 4000) developed mesothelioma between 1974 and 1978.

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69 Male Mesotheliomas with Dated Asbestos Exposure Diagnosed in Los Angeles County in 1974-1978

Year first exposed	Age at first exposure to asbestos							
	16-20	21-25	26-30	31-35	36-40	41-45	over 45	Total
1915-1919	1	0						1
1920-1924	3	0	1					4
1925-1929	2	1	2	0				5
1930-1934	0	0	1	1	0			2
1935-1939	3	1	4	1	0	0		9
1940-1944	1	3	1	1	2	0	0	8
1945-1949	1	4	0	2	2	3	1	13
1950-1954	1	0	1	2	0	0	0	4
1955-1959	0	1	1	0	1	0	0	3
1960-1964	0	0	0	0	0	1	0	1
1965-1969	0	0	0	0	0	0	1	1
Total except WW II shipyard	12	10	11	7	5	4	2	51
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Table 3
Mesothelioma Incidence per Million per year in the United States in 1970-1976, and in Los Angeles in 1974-1978

	Male		Female	
Age	United States[a]	Los Angeles	United States[a]	Los Angeles
10-19	0.0 (0)[b]	0.0 (0)	0.2 (1)	0.0 (0)
20-29	0.7 (3)	0.4 (1)	0.2 (1)	0.0 (0)
30-39	3.2 (9)	0.0 (0)	1.2 (4)	2.9 (6)
40-49	7.0 (22)	4.6 (10)	1.6 (5)	0.9 (2)
50-59	12.3 (33)	12.1 (22)	2.6 (10)	4.6 (9)
60-69	29.9 (54)	36.3 (41)	7.8 (15)	4.3 (6)
70-79	34.7 (45)	54.9 (42)	10.9 (19)	5.9 (8)

[a]Data from Hinds (1978).
[b]Number of cases in parentheses.

FUTURE INCIDENCE DUE TO SHIPYARD EXPOSURE DURING WORLD WAR II

A high proportion of men employed in shipyards during World War II were aged 35 or more at first exposure, as younger men were often on active service. We have drawn a small random sample of former employees at the Long Beach Naval Dockyard, and within this sample 68% (17/25) of men first employed during World War II were aged 35 or more when they joined the dockyard; the youngest of the 10 who worked there for more than 3 years was aged 33. The effects of such an age distribution, with 70% of men aged over 35 at first exposure and 10% aged 25 or under, are shown in the left half of Table 4. The corresponding numbers of mesotheliomas expected in successive periods, both overall and in each age cohort, are expressed as a percentage of the number of cases diagnosed in the period 1974-1978. These figures were calculated by averaging adjacent cohorts in Table 1. Thus, for example, the predicted number in each period for men aged 25 or less is the sum of the numbers shown in Table 1 for men aged 16-20 and those aged 21-25 at first exposure multiplied by 0.10, the proportion of men aged 25 or under; for men aged 26-35 the calculation is based on the sum for ages 26-30 and 31-35, and so on. Men aged over 55 at first exposure are ignored, as their risk is negligible. The figures are standardized to sum to 100 for the period 1974-1978.

Table 4 also shows the corresponding total numbers of cases in World War II shipyard workers in the United States, assuming 800 in the period 1974-1978. The predicted total number, past and future, is 5280, of which about half have already occurred. To assess the effect of the assumed age distribution, the calculation is repeated in the right half of Table 4 for a population in which equal numbers of men were first exposed at each age from 16 to 45.

Table 4
Two Age Distributions at First Exposure to Asbestos in 1942 and Corresponding War II Shipyard Workers Assuming 800 Cases in 1974-1978.

	Age at first exposure					
	16-25	26-35	36-45	46-55	Total	
	Proportion of men					
	.10	.20	.35	.35	1.00	
Year of diagnosis	Predicted numbers of mesotheliomas					WW II shipyard workers
1949-1953	0	1	1	1	3	24
1954-1958	1	2	4	3	10	80
1959-1963	3	6	9	8	26	208
1964-1968	7	13	19	13	52	416
1969-1973	13	23	31	10	77	616
1974-1978	22	36	42	–	100	800
1979-1983	33	49	28	–	110	880
1984-1988	44	58	–	–	102	816
1989-1993	54	35	–	–	89	712
1994-1998	58	–	–	–	58	464
1999-2003	33	–	–	–	33	264
Total up to age 80:					660	5280

The older distribution (left side of the table) may be more representative of the war- seems more characteristic of other industries. All figures except the World War II shipyard

Surprisingly, the predicted total number is increased by only 25%, to 6624. Therefore, it appears that the only critical assumption underlying these projections is that about 20% of currently diagnosed male cases are due to World War II shipyard exposure. There are certainly areas in which this is not true, notably Tidewater, Virginia, where 77% of mesotheliomas had been shipyard workers, and almost 40% were first exposed during World War II (Tagnon et al. 1980). In this area, however, the incidence of mesothelioma was approximately four times the national rate among white males, due to the extraordinarily high level of shipyard employment. Thus, we are inclined to believe that Los Angeles is more typical of the national average. The total number of mesotheliomas diagnosed among World War II shipyard workers is unlikely to exceed 7000, and could be considerably less.

FUTURE INCIDENCE DUE TO ASBESTOS EXPOSURE OTHER THAN IN WORLD WAR II SHIPYARDS

The figures in Table 1 give estimates of past and future numbers of cases in relation to the number currently occurring in each birth cohort according to age

Predictions of Total Numbers of Mesotheliomas in Successive Periods in World

	Age at first exposure					
	16-25	26-35	36-45	46-55	Total	
	Proportion of men					
	.25	.25	.25	.25	1.00	
Year of diagnosis	Predicted numbers of mesotheliomas					WW II shipyard workers
1949-1953	1	1	0	0	2	16
1954-1958	2	2	2	2	8	64
1959-1963	6	6	5	4	21	168
1964-1968	13	13	11	7	44	352
1969-1973	25	23	17	6	71	568
1974-1978	42	35	23	—	100	800
1979-1983	63	48	16	—	127	1016
1984-1988	85	56	—	—	141	1128
1989-1993	104	34	—	—	138	1104
1994-1998	112	—	—	—	112	896
1999-2003	64	—	—	—	64	512
Total up to age 80:					828	6624

time recruitment pattern in shipyards. The right side of the (uniform) age distribution workers columns are expressed as percentages of the 1974-1978 total.

at first exposure, but they also can be interpreted as estimates of the distribution of the numbers that would have been expected to occur in 1974-1978 for each cell in Table 2 if equal numbers of men at each age up to 45 had been first exposed under uniform conditions in each quinquennium since 1915. The figures in Table 1 are rearranged in this way in Table 5, together with the observed numbers of cases other than World War II shipyard workers from Table 2. The standardization constant used in calculating the numbers in Table 1 was chosen to make their sum equal the observed number, 20, among nonshipyard workers first exposed at age 45 or below since 1945. They can thus be interpreted as the numbers that would be expected subject to the exposure conditions of post-War recruits. The ratios of observed to expected in each row of Table 5 provide estimates of the relative "levels of exposure" of men first exposed at ages 16-20, 21-25, 26-30, 31-35, 36-40, and 41-45 in each period, while differences between the total ratios for different periods (right-hand column in Table 5) indicate secular changes in exposure. (Level of exposure is formally defined in the Appendix. It depends on asbestos dust level and duration of subsequent exposure as well as on the number of men first exposed in each age range and period.)

Table 5
Male Mesotheliomas with Recorded Asbestos Exposure Diagnosed in Los Angeles County in 1974-1978

Year first exposed	Age at first exposure to asbestos: 16-20 O[a]	16-20 E[b]	21-25 O	21-25 E	26-30 O	26-30 E	31-35 O	31-35 E	36-40 O	36-40 E	41-45 O	41-45 E	Total O	Total E
1915-1919	1	10.2	0[c]										1	10.2
1920-1924	3	10.3	0	7.5	1[c]								3	17.8
1925-1929	2	9.1	1	7.4	2	5.4	0[c]						5	21.9
1930-1934	0	7.2	0	6.3	1	5.1	1	3.7	0[c]				2	22.4
1935-1939	3	5.2	1	4.8	4	4.2	1	3.4	0	2.5	0[c]		9	20.0
1940-1944	1	3.4	3	3.2	1	3.0	1	2.6	2	2.1	0	1.6	8	15.9
1945-1949	1	2.0	4	2.0	0	1.9	2	1.7	2	1.5	3	1.2	12	10.3
1950-1954	1	1.1	0	1.1	1	1.0	2	1.0	0	0.9	0	0.8	4	5.8
1955-1959	0	0.5	1	0.5	1	0.5	0	0.5	1	0.4	0	0.4	3	2.7
1960-1964	0	0.2	0	0.2	0	0.2	0	0.2	0	0.2	1	0.2	1	1.0
1965-1969	0	<0.1	0	<0.1	0	<0.1	0	<0.1	0	<0.1	0	<0.1	0	0.2
Total 1945-1969	2	3.8	5	3.7	2	3.6	4	3.4	3	3.0	4	2.6	20	20.0

Cases first exposed after age 45 are omitted.
[a]O = Observed (see text for explanation).
[b]E = Expected from Table 1 (see text for explanation).
[c]Men with the median ages and year of first exposure corresponding to these cells would be aged over 80 during the survey period [1974-78]. The one observed case is omitted from the total in the right-hand column.

Separate predictions of past and future numbers of cases could in principle be calculated for each cell in Table 5 (see Appendix of this paper), but as the observed distribution of cases more or less conforms to the pattern of expected numbers for each age range up to age 45 in each period of first exposure since 1945, it seems more sensible merely to observe that our data suggest a fairly uniform distribution of age at first exposure (or, more correctly, level of exposure at each age) over this period and show no evidence of any change in extent of exposure since 1945. A reasonable prediction of future numbers of cases originating in exposure in each period since 1945 thus can be calculated directly from the pattern shown in the right half of Table 4, which corresponds to a uniform initial age distribution. If conditions have not altered since 1945, the same number of cases will arise in men first exposed in each successive quinquennium, possibly up to 1960-1964 or even later. The ratios of observed to expected in Table 5 are very much lower than unity before 1945, however, indicating considerably lower exposure than in 1945 or later. The ratio of observed to expected for all periods of first exposure from 1915 to 1934 is 11/72.3, or 15%, and 17/35.9, or 47%, for 1935-1944. There are too few cases to provide separate estimates for each age and period, and we have assumed that cases caused by first exposure in each 5-year period from 1915 to 1944 will also follow the pattern shown in the right half of Table 4, and that the total for each 5-year period from 1915-1919 to 1930-1934 will be 15% of the total for 1945-1949 or later, and 47% for 1935-1939 and 1940-1944. The calculation is shown in Table 6. The predicted numbers are standardized to give a total in 1974-1978 of 2240 due to asbestos exposure other than in World War II shipyards, and thus represent the overall numbers for the whole United States.

OVERALL INCIDENCE

The projection in the left half of Table 4 for World War II shipyard exposure, the right-hand column of Table 6 for other exposure, and a constant incidence of 960 cases per quinquennium unrelated to asbestos exposure, give the overall projections of total numbers of cases shown in Table 7. [If the age-specific incidence of unexposed cases remains constant, the annual number will in fact rise, as the average age of the U.S. population is still increasing. This effect has been ignored.] The least reliable aspect of these predictions is the suggestion that the eventual number of mesotheliomas in men first exposed in 1960-1964, and perhaps even 1965-1969, may be as high as for 1945-1949. Only eight cases in our survey were first exposed between 1950 and 1964, and our projections for 1950 onwards could be too high or too low by a factor of 2. The pattern of exposure levels (ratios of observed:expected in Table 5) suggested by our data, increasing from 15% before 1935 to 100% by 1945 and subsequently remaining at about this level until 1965 or later, corresponds reasonably close to total U.S. asbestos consumption, however (Fig. 1, shown on page 63), and industrial exposure was probably not controlled effectively in many areas until about 10 years ago.

Table 6
Projections of Past and Future Numbers of Male Mesotheliomas in the United States due to Asbestos Exposure, Excluding World War II Shipyard Workers

	Assumed "level of exposure"									
	0.15	0.15	0.15	0.15	0.47	0.47	1.00	1.00	1.00	1.00
	Period first exposed									
Year of diagnosis	1915-1919	1920-1924	1925-1929	1930-1934	1935-1939	1940-1944	1945-1949	1950-1954	1955-1959	1960-1964	Total
1924-1928	2										2
1929-1933	8	2									10
1934-1938	22	8	2								32
1939-1943	46	22	8	2							78
1944-1948	75	46	22	8	7						158

1949-1953	105	75	46	22	26	7					281
1954-1958	134	105	75	46	69	26	14				469
1959-1963	149	134	105	75	145	69	56	14			747
1964-1968	145	149	134	105	234	145	148	56	14		1130
1969-1973	118	145	149	134	330	234	309	148	56	14	1637
1974-1978	67	118	145	149	419	330	499	309	148	56	2240
1979-1983		67	118	145	466	419	703	499	309	148	2874
1984-1988			67	118	456	466	892	703	499	309	3510
1989-1993				67	370	456	991	892	703	499	3978
1994-1998					211	370	970	991	892	703	4137
1999-2003						211	787	970	991	892	3851
2004-2008							450	787	970	991	3198
2009-2013								450	787	970	2207
2014-2018									450	787	1237
2019-2023										450	450
Total	871	871	871	871	2733	2733	5819	5819	5819	5819	32,226

The figures are standardized to give a total of 2240 cases in 1974-1978.

Table 7
Overall Projections of Numbers of Mesotheliomas Diagnosed in the United States in Successive Periods in Men First Exposed to Asbestos before 1965, or Unexposed

	World War II shipyards	Other asbestos exposure	Unexposed	Total
1924-1928		2	960	962
1929-1933		10	960	970
1934-1938		32	960	992
1939-1943		78	960	1038
1944-1948		158	960	1118
1949-1953	24	281	960	1265
1954-1958	80	469	960	1509
1959-1963	208	747	960	1915
1964-1968	416	1130	960	2506
1969-1973	616	1637	960	3213
1974-1978	800	2240	960	4000
1979-1983	880	2874	960	4714
1984-1988	816	3510	960	5286
1989-1993	712	3978	960	5650
1994-1998	464	4137	960	5561
1999-2003	264	3851	960	5075
2004-2008		3198	960	4158
2009-2013		2207	960	3167
2014-2018		1237	960	2197
2019-2023		450	960	1410
1924-2023	5,280	32,226	19,200	56,706

THE ETIOLOGY AND AGE DISTRIBUTION OF INCIDENTAL CASES

The multistage model of carcinogenesis provides a qualitative, and sometimes quantitative, explanation for a variety of observations on spontaneous and induced cancer rates in both animals and humans, and of cellular transformation rates in various in vitro systems. In its simplest form, such a model predicts that exposure to an initiator (a carcinogen effecting the first change in a multistage process) is likely to increase cancer incidence in approximate proportion to some power of time since first exposure, irrespective of age at first exposure, and that the incidence of spontaneous tumors of the same type will be proportional to age raised to the same power. An example of such relationships is provided by lung cancer rates in smokers and nonsmokers. Lung cancer incidence appears to be approximately proportional to the 4th or 5th power of duration of smoking among continuing cigarette smokers, irrespective of age,

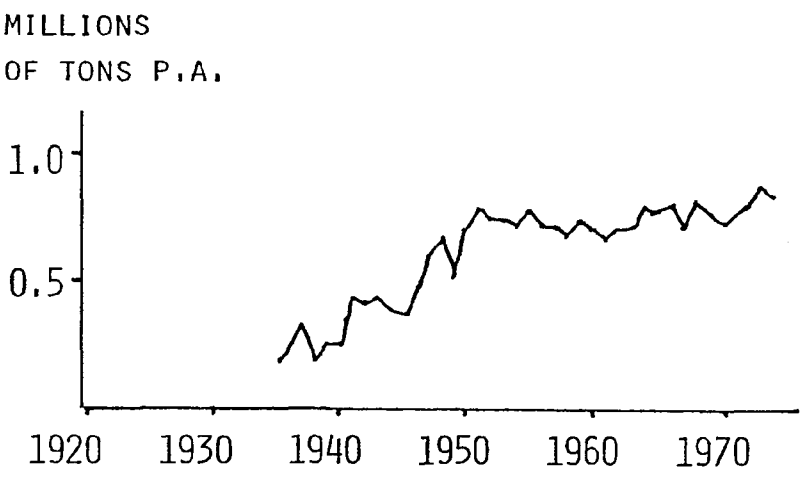

Figure 1
Total U.S. asbestos consumption

and to more or less the same power of age in nonsmokers (Doll 1978). This suggests: (1) that smoking increases the frequency of the first of an ordered (or at least partially ordered) sequence of changes involved in the transformation of a normal cell to malignancy, and (2) that the rates at which these cellular changes occur are not strongly age dependent.

The close analogy between these observations and the incidence pattern of asbestos-induced mesothelioma, for which incidence is proportional to (time since first exposure)$^{3.5}$, suggests that the incidence in individuals who have not been exposed to asbestos might be expected to rise as (age)$^{3.5}$. That this is approximately so is shown in Table 8, where the age distribution of the 22 male and 19 female cases in our survey who were reported as unexposed is compared with the distribution that would have been expected if incidence were proportional to (age)$^{3.5}$.

The assumption that cases reporting no asbestos exposure are really spontaneous, and will therefore persist at the current level, is supported by the similar incidence in men (22 cases) and women (19 cases), although they could be due to ambient asbestos exposure, which presumably would affect the sexes equally. A more banal explanation is that many are not mesotheliomas at all. Preliminary results of a pathological review of our material suggest that the diagnosis will be revised in a significantly higher proportion of "unexposed" cases than of those with a history of asbestos exposure. Their inclusion in future projections, and the suggestion that such cases follow the age-incidence curve that might be expected by analogy with lung cancer rates in smokers and nonsmokers, must therefore be regarded as provisional.

Table 8
Age Distribution of Unexposed Mesothelioma Cases Diagnosed in Los Angeles County, 1974-1978, and Population in Thousands

	Age								
	20-	30-	40-	50-	60-	70-	80-	90-94	Total
Men									
number	1	0	3	3	8	5	2	0	22
Los Angeles population	540	423	435	365	226	112	38	3	2142
Women									
number	0	3	2	5	6	1	1	1	19
Los Angeles population	575	418	458	394	280	185	76	8	2394
Both sexes									
number	1	3	5	8	14	6	3	1	41
Los Angeles population	1115	841	893	759	506	297	114	11	4536
expected	0.8	1.9	4.7	8.1	9.7	9.4	5.6	0.7	41.0

Expected numbers are based on the assumption that incidence is proportional to age$^{3.5}$.

DISCUSSION

The accuracy of our predictions relating to particular periods, notably the effects of World War II shipyard exposure, depends on the assumption that Los Angeles is typical of the rest of the United States. The method appears to be surprisingly robust even against substantial variation in the assumed distribution of age at first exposure, however, and as we have standardized our predictions to correspond to current national rates, any underestimation of numbers originating in a particular period or industry is at least partially compensated by a corresponding overestimate elsewhere. The overall prediction, at least for the effects of first exposure before 1950, is unlikely to be much in error. Our estimate of 5280 mesotheliomas due to World War II shipyard exposure, together with less than 3000 due to other exposure during World War II, is less than 3% of the lowest estimate of future numbers due to past asbestos exposure in the estimates paper of Bridbord et al. (1978). This report predicted that previous asbestos exposure, principally during World War II, would eventually cause at least 280,000 mesothelioma deaths, but the calculations were not presented in sufficient detail for the effects of World War II and later exposure to be separated.

The predictions relating to first exposure after 1945 are necessarily speculative, but they are of some value, if only to indicate that although there is a growing epidemic of asbestos-related disease, the incidence may never much exceed the current rate, and is unlikely to double. A national study conducted and analyzed along the lines of this paper is evidently needed. Such a survey would provide more precise estimates of the effects of exposure in various periods, particularly between 1950 and 1965 where our data are most sparse, and definitive data on shipyard workers.

It is difficult to know what adjustment, if any, should be made to allow for misdiagnosis. In our view, the disease is usually diagnosed in asbestos workers, but it may never be possible to establish the true incidence. We have not discussed the incidence due to asbestos exposure among women. Twenty-one percent of the cases diagnosed in Los Angeles County were women, but the majority had had no known exposure (19/25 interviewed). Three had been exposed at work (one only 3 years before the disease was diagnosed), two had been married to asbestos workers, and one reported childhood exposure. It is not yet possible to distinguish a secular increase in incidence among women from the effects of improving diagnosis in the United States, but in England the female rate has not increased much since 1967, while the reported incidence in men has doubled (Acheson and Gardner 1979). Thus, it seems unlikely that the incidence among women will ever much exceed the current relatively low level, although the possibility remains that substantial numbers of women were first exposed since 1950.

The lifelong risk of mesothelioma following asbestos exposure is very low among men first exposed after age 40, but for lung cancer the relative risk, and hence the lifelong risk, does not change markedly with age at first exposure (Peto 1979; Seidman et al. 1979). The overall excess of lung cancer among men who have been exposed industrially to asbestos has in most studies been of the order of three times the number of mesotheliomas (McDonald and McDonald, this volume), but this ratio may be higher among World War II employees, many of whom were considerably older at first exposure than most earlier or later recruits. If our predictions of approximately 5000 mesotheliomas in men first exposed in shipyards and 3000 for other industries in World War II are correct, the excess number of lung cancers could exceed 30,000. The "mesothelioma epidemic" is the most obvious manifestation of World War II exposure, as the disease is normally so rare, but it may be a relatively minor component of the resulting morbidity and mortality.

The predicted number of mesotheliomas caused by asbestos in men first exposed in the U.S. at any time before 1965 shown in Table 7 is about 37,500, and a corresponding excess of lung cancer of about three times this figure implies a total of about 150,000 cancer deaths, most of which have yet to occur. The extent of wartime asbestos exposure may have been exaggerated, but the effects of later exposure, which are only beginning to be seen, may prove considerably greater than has been generally realized.

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APPENDIX

The excess cancer incidence caused by a specific pattern of carcinogenic exposure will in general increase with increasing dose, but the time-dependence is usually independent of dose. In other words, for some functions D and f

$$\text{incidence} = D(d) \cdot f(a,t) \quad (1)$$

at age a following a specified pattern of exposure at dose d starting at age t. (This equation cannot, in general, be applied to a group of individuals who have suffered different patterns of exposure. For example, a smoker who increased his consumption steadily from 10-20 cigarettes per day over 10 years and then stopped smoking has suffered double the dose of one who increased from 5-10 cigarettes per day over the same period and then stopped, but his dose cannot be compared directly with that of a continuing smoker, whose incidence will follow a quite different time course.) For industrial carcinogens, usually it is not possible to obtain accurate enough data on either dose or incidence to establish the form of D, the dose dependence. For the purposes of the present analysis, however, we shall define D as the "effective dose," thereby guaranteeing linearity, and write (1) as

$$\text{incidence} = D \cdot f(a,t). \quad (2)$$

This formulation, in which dose-response is by definition linear, greatly simplifies the analysis. Exposure levels are poorly measured and vary widely, but for a specific pattern of exposure the overall incidence in a cohort of individuals who were first exposed at the same time and age can also be described by equation (2), the constant factor D now denoting the average "effective dose" of the cohort. (The selective loss of the most heavily exposed individuals would in fact progressively reduce D, the average exposure of the survivors. This relatively minor effect is ignored.)

National Incidence

Ignoring those who have never been exposed to asbestos, the general population can be divided into cohorts on the basis of age at first exposure and period of first exposure to asbestos. Thus C_{ij} denotes the cohort first exposed in year i at age j. The function f specifying the time and age dependence of the resulting cancer incidence would for many carcinogens depend strongly on whether exposure was brief or continuous, and the proportions suffering various patterns of exposure might vary considerably between cohorts. For asbestos-induced mesothelioma, however, incidence appears to rise approximately as (time since

first exposure)$^{3.5}$ irrespective of age, fiber type, or exposure pattern. Denoting the average "effective dose" of cohort C_{ij} by D_{ij}, the incidence I_{ij} at age a in cohort C_{ij} will be approximately

$$I_{ij}(a) = D_{ij} \cdot (a - j)^{3.5}. \quad (3)$$

The expected number of cases $e_{ij}(a)$ occurring in unit time at age a in cohort C_{ij} will be approximately

$$e_{ij}(a) = n_{ij} \cdot D_{ij} \cdot (a - j)^{3.5} \cdot p(a)/p(j), \quad (4)$$

where $p(a)$ is the probability of surviving to age a, and n_{ij} is the number of people first exposed in year i at age j—that is, the initial size of cohort C_{ij}. The life-table p should in principle also be suffixed by i,j to take account of secular changes in national mortality and the higher mortality of those who have been exposed; but to simplify the analysis we shall ignore these effects and replace p by the life-table based on current national mortality rates. Therefore, our predictions will be somewhat inflated if, as seems likely, an appreciable proportion of mesotheliomas occur among men whose exposure was high enough to reduce life expectancy significantly.

Definition of "Level of Exposure"

Finally, equation (4) can be simplified further by combining n_{ij} and D_{ij}. It may be difficult and pointless to attempt to estimate the numbers n_{ij} who were first exposed to an agent such as asbestos at a particular age and period, as there will be great heterogeneity of exposure levels within each cohort, and the results could not be used to provide meaningful estimates of individual risk. For the purpose of analyzing the evolution of national cancer incidence, however, the product $N_{ij} = n_{ij} \cdot D_{ij}$, the average "level of exposure" of the population resulting from first exposure at age j in year i, is equally useful and more convenient. Equation (4) thus can be written

$$e_{ij}(a) = N_{ij} \cdot (a - j)^{3.5} \cdot p(a)/p(j). \quad (5)$$

To simplify the notation, it has been assumed that analysis is based on single years of age, age at first exposure, year of first exposure, and period of observation of incident cases. In practice, it is more convenient to use quinquennial divisions, a, i, and j denoting quinquennial midpoints. In particular, $e_{ij}(a_s)$ denotes the expected number of cases diagnosed in the study period (1974-1978) aged between $a_s - 2\frac{1}{2}$ and $a_s + 2\frac{1}{2}$ years among men first exposed in the quinquennia of age and period centered at age j and year i respectively. (Note that if the year i_s is the midpoint of the survey period, $a_s = j + i_s - i$ for cohort C_{ij}.) Approximating $p(a)$ by the life-table based on current national death-rates, this formula provides a basis for estimating N_{ij}, and hence the numbers of cases in each past and future quinquennium from the

present rate of occurrence in cohort C_{ij}. Moreover, the average "levels of exposure" N_{ij} of different cohorts provide a useful indication of the relative degree of overall exposure in different periods, although they do not enable us to distinguish periods in which a few individuals were heavily exposed from those in which a larger number suffered moderate exposure.

The expected numbers $e_{ij}(a_s)$ are estimated by interviewing a sample of cases to determine age and period of first exposure. A random sample of controls should, in principle, also be interviewed and the "attributable fraction" of cases estimated in the usual way in each cohort. This adjustment, which would slightly reduce the proportion of cases attributed to asbestos exposure, has not been attempted. We have simply assumed that all cases with recorded exposure were caused by asbestos and have classified the remainder as "incidental," although some, or even all, such "incidental" cases may be due to ambient asbestos or unrecorded acute exposure.

Standard Errors of Predicted Future Incidence

The most severe limitation is the inaccuracy of predictions resulting from recent exposure. This is an inevitable consequence of the time distribution of industrial cancers, which are usually rare until 20 or more years after first exposure to a carcinogen. Thus, for example, less than 1% of the total number of mesotheliomas that eventually will occur in a cohort of men first exposed to asbestos in the age range 21-25 will be diagnosed before age 40. The diagnosis of a single case in 1980 of a man born in 1942 who was first exposed in 1965 would (in expectation) imply that about 150 further cases will occur in his birth cohort, but the 95% confidence interval of this predicted number would be (4-840). In practice, of course, reasonably smooth trends over time and age will be observed and outliers can be ignored; but it is difficult to assign confidence intervals either within any particular cohort or overall.